Anisometropia in Children from Infancy to 15 Years

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PURPOSE. To investigate anisometropia in children from age 6 months to 15 years.

METHODS. Children with refractions at 6 months ($n = 1120$), 5 years ($n = 395$), and 12 to 15 years ($n = 312$) were included in this study. All children were refracted in the laboratory by noncycloplegic retinoscopy. Myopes had spherical equivalent refraction (SER) of the less ametropic eye of less than -0.50 D, hyperopes had SER of the less ametropic eye greater than or equal to 1.00 D, and emmetropes had SER of the less ametropic eye from -0.50 to $+1.00$ D.

RESULTS. The mean difference in refraction between the two eyes was similar at 6 months (0.11 D) and 5 years (0.15 D), increasing to 0.28 D at 12 to 15 years. Using a cutoff of 1.00 D SER for anisometropia, the prevalence was 1.96% , 1.27% , and 5.77% at 6 months, 5 years, and 12 to 15 years, respectively. At 12 to 15 years, the prevalence of anisometropia in the myopes was 9.64% and in the hyperopes was 13.64% , both significantly higher than that in the emmetropes (3.38% , $P < 0.05$). The degree of anisometropia at 12 to 15 years was significantly associated with the refractive error of the less ametropic eye at 12 to 15 years, with and without adjustment for relevant covariates ($P < 0.05$). Infants with significant astigmatism (cylinder power ≥ 1.00 D in one or both eyes) have an increased risk of anisometropia ($P < 0.05$).

CONCLUSIONS. The prevalence of anisometropia increases between 5 and 15 years, when some children's eyes grow longer and become myopic. However, anisometropia was found to accompany both myopia and hyperopia, suggesting that other mechanisms in addition to excessive eye growth may exist for anisometropia development, especially in hyperopia. (*Invest Ophthalmol Vis Sci.* 2012;53:3782–3787) DOI:10.1167/iovs.11-8727

Anisometropia is a condition where the refractive error differs between the two eyes. A difference in spherical equivalent refraction (SER) of 1 diopter or more (SER difference ≥ 1.00 D) is usually used as the definition for anisometropia. In the following review of the literature, most studies used this definition unless otherwise noted. Previous cross-sectional studies showed that the prevalence of anisometropia is age-dependent, with a relatively low prevalence (1.6% – 4.3%) among young children^{1–4} and a higher prevalence among adults. A study using a slightly stricter definition for

anisometropia (SER difference > 1.00 D)⁵ found a prevalence of 7.7% among adults, whereas in studies using the traditional definition, the prevalence was slightly higher, ranging from 9% to 15% .^{6–8} The trend of more anisometropia with increasing age continues after the age of 60 years, climbing from about 10% for 60- to 69-year-olds to more than 30% for 80+ years.^{5,6,8} In older people, the anisometropia might be due to differential changes in lens power and the development of cataracts. Most anisometropia appears to be axial in nature, as demonstrated in studies of both animal and human eyes reporting a positive correlation between the degree of anisometropia and the interocular difference in axial length.^{1,9–12}

Infantile anisometropia can be transient and may disappear as eyes emmetropize.^{2,13} In contrast, the Multi-Ethnic Pediatric Eye Disease Study found that the prevalence of anisometropia was low (4% – 5%) and remained almost constant between 1 and 6 years of age in both Hispanic and African American children.⁴ Severe infantile anisometropia (≥ 3.0 D) may be sustained over a long period, and children with persistent anisometropia are more likely to develop amblyopia during the preschool years.¹⁴ Studies examining the association of anisometropia and amblyopia in young children found a significant association between the two,^{3,15–19} with a low prevalence of amblyopia overall (1.5% – 2.6%),^{15,17–19} and part of it ($24\% \sim 37\%$) due to anisometropia.^{16,18}

There is limited evidence in the literature regarding the relationship between anisometropia and astigmatism. An early longitudinal study investigating refractive error change from age 1 to 3.5 years found that young children with significant astigmatism were more likely to be anisometric ($+1.00$ D sphere and/or $+1.00$ D cylinder difference between the two eyes) compared with those without astigmatism.²⁰ This result was echoed in elderly adults (50+ years) of the Blue Mountains Eye Study (BMES).⁶ In addition, higher proportions of anisometropia have been reported in populations with more astigmatism,^{13,21} an association that seems to be largely independent of age.

A few longitudinal studies showed that anisometropia increases after children start school. A study in Japan found a small increase in the prevalence of spherical anisometropia (spherical difference ≥ 1.00 D), rising from 1.43% at 6 years to 3.14% at 11 years.²² In addition, a similar increase in the prevalence of astigmatic anisometropia (cylinder difference ≥ 1.00 D), from 2.6% at 6 years to 4.3% at 11 years, was also found in that study.²² Two other longitudinal studies in more myopic schoolchildren found larger increases (6% and 10% increase, respectively) in the prevalence of anisometropia after 3 years of follow-up.^{23,24} An additional finding of the two studies was a link between myopia and anisometropia. Using data from children participating in a randomized trial of myopia treatment, Pärssinen²³ found a significant association between the increase in the amount of anisometropia (spherical equivalent) and myopia progression, but not with the refractive error at baseline. In a study of Singaporean children aged between 7 and 11 years, a significantly higher amount of anisometropia was found in myopes versus nonmyopes.²⁴ There was also a significant association between

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Supported by National Eye Institute, National Institutes of Health, Grants EY01191 and EY018694.

Submitted for publication October 3, 2011; revised February 9, April 3, and May 3, 2012; accepted May 8, 2012.

Disclosure: L. Deng, None; J.E. Gwiazda, None

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anisometropia and more myopia progression, but no association between myopia at baseline and change in anisometropia over the 3 years of follow-up.²⁴ Even though these studies provided evidence for an association between myopia and anisometropia, the exact etiology of anisometropia and its possible link to the mechanisms underlying refractive error development remain elusive. Evidence on the relationship between anisometropia and refractive error over time during childhood is generally lacking and is needed to help answer these questions.

Using data from children recruited for a previous long-term study of refractive error and visual function development, our study investigated how anisometropia develops during childhood and changes over a wide age range, from infancy to 15 years; how anisometropia in teenagers relates to refractive characteristics in infants and preschoolers; how anisometropia in early childhood relates to later myopia development; how anisometropia relates to astigmatism in infancy; and also investigated asymmetry in the refraction difference between the two eyes at 12 to 15 years.

METHODS

Subjects and Procedures

All data were taken from a previous long-term study of visual development and refractive error initiated at the Massachusetts Institute of Technology in 1975 and continued at the New England College of Optometry until 2006. The research was initially designed as a series of short-term studies on normative visual development in young children, which required follow-up visits in the early years of life. Later studies focused on risk factors for development of myopia in school-age children, which included many of the earlier participants returning for visits. The refraction records of participants with recurrent visits formed our longitudinal dataset. Most subjects (~95%) were white and the sex distribution was well balanced. Children were refracted by noncycloplegic near retinoscopy before 3.5 years of age and by noncycloplegic distance retinoscopy after 3.5 years. The noncycloplegic refraction method was chosen to increase the recurrent visit rates for longitudinal measurements. Over the 32 years of our study, only three experienced optometrists performed the refractions: Dr Indra Mohindra, Dr Mitchell Scheiman, and Dr Frank Thorn. The noncycloplegic near retinoscopy was performed in a dark room at a fixed distance of 50 cm. An adjustment factor of -1.25 D was added to the spherical component to account for the 50-cm working distance minus tonic accommodation. In addition, Dr Thorn, who refracted most of the young children, used a variation of the near retinoscopy technique by waiting longer for children's accommodation to relax and then using the most hyperopic reading during a test session. Details of subject recruitment,²⁵ the optometrists who performed the refractions over the years,²⁶ and the refraction procedures have been described previously.²⁵⁻²⁷

An informed written consent form was signed by either a parent or legal guardian of each subject. The project was approved by the institutional review boards at both institutions, and it adhered to the tenets of the Declaration of Helsinki. Refraction data of both eyes from children with records at 6 months (3–9 months), 5 years (4.51–5.50 years) and/or 12 to 15 years were included in the data analysis.

Statistical Analysis

The refraction was taken as the SER by adding the spherical component and half of the cylinder power (in negative sign). The absolute difference in SER between the two eyes was used as the degree of anisometropia on a continuous scale. Two cutoffs were applied to define the categorical variable anisometropia: (1) SER difference between the eyes greater than or equal to 1.00 D and (2)

SER difference between the eyes greater than or equal to 0.50 D, so as to ensure the robustness of the findings. The prevalence of anisometropia by age was computed as the proportion of children with anisometropia using both definitions within an age group.

The refraction of the less ametropic eye (more emmetropic eye) was used to define the refractive groups. Myopes refer to children with SER less than -0.50 D in the less ametropic eye, hyperopes refer to children with less ametropic SER greater than or equal to 1.00 D, and emmetropes refer to children with less ametropic SER between -0.50 D and less than 1.00 D. When refractive error is treated as a continuous variable in the following analyses, it refers to the SER of the less ametropic eye. Significant astigmatism is defined as having 1.00 D or more cylinder power in one or both eyes.

Spearman correlations were computed between the degree of anisometropia at 6 months versus 12 to 15 years and 5 years versus 12 to 15 years. Correlations were also computed between the degree of anisometropia at 6 months or 5 years and ametropia at 12 to 15 years. Simple and multiple linear regression were run to examine the associations of the degree of anisometropia at 12 to 15 years with other refractive characteristics, including refractive error, cylinder power, anisometropia at early ages (6 months and 5 years) and refractive error and cylinder power at 12 to 15 years, using data from children with refraction records at all three visits. The odds ratio (OR) with the 95% confidence interval (CI) was computed to test the association between anisometropia and myopia or hyperopia at 12 to 15 years. The chi-square test was conducted to test the association between astigmatism and anisometropia in infancy, with all the variables treated as categorical data. Bland-Altman plots were used to examine a possible asymmetry in the refraction between the left and right eye. Statistical significance was taken as P less than 0.05.

RESULTS

Anisometropia, Refractive Error, and Their Correlation by Age

A total of 1120 children had refraction data at 6 months; at 5 years 395 children had data; and at 12 to 15 years 312 had refraction records. The mean SER and the mean difference in SER between the two eyes by age are listed in Table 1. As shown in the table, there was a clear myopic shift in the refraction over time, decreasing from 1.00 D in infancy to -0.42 D in the early teen years. The mean intereye difference in SER was small (0.11 D) at 6 months and 5 years (0.15 D) and nearly doubled from 5 years to 15 years (0.28 D). The prevalence of anisometropia (difference in SER ≥ 1.00 D) was similarly low during infancy and at 5 years (1%–2%) and

TABLE 1. Mean Refraction, Amount of Anisometropia, and Prevalence of Anisometropia by Age

	Age		
	6 Months	5 Years	12–15 Years
Total no. subjects	1120	395	312
Average SER of OD and OS (mean $\pm$ SD)	1.0 $\pm$ 1.18D	0.75 $\pm$ 0.99D	-0.42 ± 1.75 D
Difference in SER between eyes (mean $\pm$ SD)	0.11 $\pm$ 0.25D	0.15 $\pm$ 0.29D	0.28 $\pm$ 0.47D
SER difference ≥ 0.50 D (%)	101 (9.02)	34 (8.61)	63 (20.19)
SER difference ≥ 1.00 D (%)	22 (1.96)	5 (1.27)	18 (5.77)

FIGURE 1. Prevalence of anisometropia by age.

increased to 5.77% at 15 years, as shown in Figure 1. A similar temporal trend holds when the 0.50 D cutoff is used.

Categorical data analysis was conducted to examine the association between anisometropia and refractive errors in the teen years. As illustrated in Figure 2, myopes and hyperopes had higher proportions of anisometropia (SER difference ≥ 1.00 D) ($8/83 = 9.64\%$ and $3/22 = 13.64\%$, respectively) compared with emmetropes ($7/207 = 3.38\%$), showing a “U” shape in the prevalence of anisometropia across the three refractive groups. The risks of having anisometropia (SER difference ≥ 1.00 D) were significantly higher in myopes and hyperopes compared with emmetropes (ORs = 3.05 [95% CI 1.07, 8.70], and 4.51 [1.08, 18.89], respectively). As shown in the figure, the pattern remains the same when the cutoff for anisometropia is 0.50 D. The risks of having anisometropia (SER difference ≥ 0.50 D) were significantly higher in myopes versus emmetropes (OR = 2.36 [1.29, 4.30]), but fell short of significance for the comparison between hyperopes and emmetropes (OR = 2.05 [0.75, 5.64]).

Correlation between the Degree of Anisometropia at Early Ages and the Degree of Anisometropia/Refractive Error at Later Ages

Longitudinal datasets were constructed using the data reported in the previous section. A total of 190 children had refraction data at both infancy and 12 to 15 years and 211 children had

FIGURE 2. Anisometropia among 12- to 15-year-olds by refractive group.

refraction data at both 5 years and 12 to 15 years. The degree of anisometropia in infancy was not correlated with either the degree of anisometropia or SER at 12 to 15 years ($r = -0.01$ and 0.08 , respectively, $P > 0.05$). In comparison, the correlation between the degree of anisometropia at 5 years and 12 to 15 years was slightly larger and significant ($r = 0.14$, $P = 0.0496$); however, no relationship was found between the degree of anisometropia at 5 years and SER at 12 to 15 years ($r = 0.03$, $P = 0.71$).

Association of the Degree of Anisometropia at 12 to 15 Years with Other Refractive Characteristics

The results of simple and multiple linear regression, examining the associations of the degree of anisometropia at 12 to 15 years with other refractive characteristics using the longitudinal dataset of children with refraction records at all three visits ($n = 140$), are shown in Table 2. The degree of anisometropia at 12 to 15 years was not significantly associated with any refractive characteristics at 6 months (all $P \geq 0.18$) with or without adjustment, similar to the results reported previously. The degree of anisometropia at 12 to 15 years was significantly associated with the SER in the less ametropic eye at 5 years ($P = 0.02$), but not with the degree of anisometropia or cylinder power at 5 years, after adjusting for the other characteristics (both $P > 0.23$). In addition, at 12 to 15 years the degree of anisometropia was significantly associated with the refraction of the less ametropic eye ($P = 0.002$), but not the cylinder power ($P = 0.32$) after adjustment.

Comparison of Characteristics between Children Who Remained in the Longitudinal Study Versus Those Lost to Follow-up

The baseline characteristics of infants who remained in the longitudinal study up to 12 to 15 years were compared with those for infants who were lost to follow-up. There were no significant differences in the amount of refractive error or the degree of anisometropia at baseline between the two groups (both $P > 0.05$); however, children with longitudinal follow-up had slightly more cylinder power than those who did not (-1.10 D vs. -0.87 D, $P = 0.006$).

Anisometropia and Astigmatism in Infancy

Of the 1120 infants, 464 (41.43%) had significant astigmatism (cylinder power 1.00 D or above in one or both eyes), similar to what has been reported previously using an earlier version of the same dataset.²⁵ At the age of 5 years, the proportion of

TABLE 2. Relationship of Refractive Characteristics at 6 months, 5 years, and 12 to 15 Years to the Degree of Anisometropia at 12 to 15 Years

Covariates	Unadjusted		Adjusted	
	Slope	P Value	Slope	P Value
6-mo SER (LAE)	−0.002	0.949	0.002	0.949
6-mo cylinder power	0.036	0.312	0.025	0.183
6-mo anisometropia	−0.011	0.946	−0.010	0.953
5-y SER (LAE)	0.055	0.309	0.160	0.020
5-y cylinder power	−0.143	0.221	−0.116	0.335
5-y anisometropia	0.328	0.176	0.294	0.234
12–15-y SER (LAE)	−0.054	0.013	−0.086	0.002
12–15-y cylinder power	−0.188	0.011	−0.084	0.320

P values in bold and italic are significant at the 0.05 level.
LAE, less ametropic eye.

FIGURE 3. Association between anisometropia and significant astigmatism in infants.

children with significant astigmatism was much smaller ($34/395 = 8.61\%$) and increased slightly for the age group 12 to 15 years ($33/312 = 10.58\%$). The prevalence of anisometropia (SER difference ≥ 1.00 D) in infants with significant astigmatism was slightly but significantly higher than in those without (left section of Fig. 3, 3.02% vs. 1.22% ; $P = 0.03$). A similar association was observed if a lower threshold for anisometropia (0.50 D) was used, 12.93% vs. 6.25% for infants with and without significant astigmatism (right section of Fig. 3, chi-square $P < 0.0001$).

Asymmetry of the Ametropia

The mean refraction at 12 to 15 years was -0.45 ± 1.77 D for the left eye and -0.39 ± 1.78 D for the right eye. The difference in SER between eyes was not significantly different from zero, indicating no asymmetry in the direction of ametropia. As shown in the Bland-Altman plot (Fig. 4), the differences in SER between eyes exhibit no sign of a systematic shift toward either the left eye or the right eye.

DISCUSSION

In this study, we found that the prevalence of anisometropia at early ages (6 months and 5 years) was consistently low (1% – 2%) but increased to 5.8% by the age of 15 years. We also found

FIGURE 4. Interocular difference in refractive error at 12 to 15 years.

a positive association between anisometropia and ametropia (either myopia or hyperopia) at 15 years.

The prevalence of anisometropia increased from the preschool years to 15 years in our study, which is in accord with the increase reported in two longitudinal studies where more myopic populations were examined.^{23,24} Other studies examining children in rural areas reported a small increase²² or no increase²¹ with age during the school years. As the refractive errors of our subjects during their school years are more similar to those in Singapore and Finland,^{23,24} an increase in the prevalence of anisometropia is not surprising. These two longitudinal studies also found some relationship between anisometropia and myopia progression, with faster progression accompanied by a greater increase in anisometropia. Our finding that anisometropia at an early age had no influence on myopia in the teenage years suggests that anisometropia is not a cause of myopia.

Another interesting result of this study was that not only myopes but also hyperopes were more likely than emmetropes to have anisometropia, using 1.00 D as the cutoff. Similar to this result, Qin et al.⁸ found symmetry of anisometropia centered around the emmetropic state with higher degrees of anisometropia with larger refractive errors in 20- to 99-year-old patients. A similar association between ametropia (either hyperopia or myopia) and anisometropia among older adults ($50+$ years) was also observed in the BMES,⁶ where the mean degree of anisometropia increased with the amount of refractive errors in both directions. The nature of this association may differ from the one found in our study, as age-related eye disease, such as cataracts, may play a role in anisometropia development in an older population.

Most anisometropia is attributed to the difference in axial length between the eyes. In experimentally induced anisometropia, the refraction difference is highly correlated with the difference in axial length, implying that the induced anisometropia is axial in nature.^{9,10} Significant correlations/associations between interocular axial length differences and anisometropia have also been found in human studies.^{1,11,12} Although the association between differences in refraction and axial length has been confirmed in many studies, how anisometropia develops and what triggers different growth rates between the two eyes are still unclear. Abnormal visual input in one eye may cause more axial elongation in that eye, as demonstrated in animal studies of various species.^{9,10,28} Defects in the structure of the optical components due to prematurity^{29,30} or cataracts³¹ could also result in significant differences in refraction. For children without obvious structural problems in their eyes, however, like the participants in our study, other mechanisms must be involved.

The pattern of anisometropia development in children appears to reflect changes in SER that have been reported to occur at different ages. During the first several years of life, a relatively wide distribution of mostly positive refractive errors is narrowed down to a tight distribution with a slightly hyperopic mean SER while the degree and prevalence of anisometropia remain almost constant.

A later phase of refractive development occurs around the time of myopia onset (7 – 12 years). The refractive errors of many children shift toward the myopia direction, resulting in a wider spread of refractive errors and development of significant intereye differences in refraction. This anisometropia may reflect a difference in the rate of eye growth between the two eyes; however, this mechanism may not apply to hyperopia because in that refractive condition there is more limited eye growth. The lack of axial length data in the present study limits our ability to differentiate the mechanisms for anisomyopia and anisohyperopia development.

As SER depends on both spherical and cylindrical power, mismatches in either or both components between the two eyes could lead to significant anisometropia. Many studies have shown a link between anisometropia and astigmatism, as was found in our study. The BMES study⁶ found a linear trend between the cylinder power and anisometropia (defined by the difference in SER). A significant association of anisometropia and astigmatism in young children has also been reported.^{20,32} In addition, some studies examining anisometropia in populations with significant astigmatism^{13,21} have reported relatively higher percentages of anisometropia than studies of subjects with little or no astigmatism.^{1,4,22} Our results agree with these findings in that infants with astigmatism in one or both eyes had a slightly higher percentage of anisometropia. Like previous studies,^{33–35} our study found a high prevalence of astigmatism (cylinder power ≥ 1.00 D) in infancy and then a decline to the preschool age. A recent study on changes in refractive astigmatism, as well as in corneal astigmatism, from 6 months to 8 years in Native American children³⁶ suggested that the change in refractive astigmatism in early childhood was at least partially due to a change in corneal astigmatism. The between-eye differences in corneal astigmatism were implied to be the cause of aniso-astigmatism in an Australian study among 6-year-olds.¹ How much the change in corneal astigmatism in infancy is related to the changes in astigmatism and anisometropia during childhood remains unknown, as these previous studies were not longitudinal and we did not measure corneal astigmatism.

No asymmetry in refraction was noted in our study. A relationship between eye dominance and anisometropic myopia was reported in some studies, with the dominant eye being more myopic,^{37,38} whereas another study with a large sample size had an opposite result.³⁹ As no information on ocular dominance was collected in our sample, confirmation of a similar association could not be carried out.

In addition to having no information on eye dominance, there are other limitations of our study. The noncycloplegic refraction method was used in our study. However, the proportion of anisometropia in our sample was within a range reported for other studies with refractions obtained with and without cycloplegia.^{1–4,20,22} This mitigates against a major role for cycloplegia. The findings regarding astigmatism are robust, as most literature suggests that the measures of astigmatism are less sensitive to cycloplegia.^{27,40,41} The second limitation was that the overall number of subjects in our study is large but when broken down by age and refractive error becomes more limited. Also, the numbers of hyperopes/emmetropes with anisometropia by the conventional definition (≥ 1.00 D) and the numbers of high myopes and hyperopes at 12 to 15 years were small, constraining the statistical strength of any associations. Finally, we do not have measurements on corneal astigmatism or axial length to differentiate mechanisms related to anisometropia and astigmatism development as children's eyes grow.

To summarize, we found a low prevalence of anisometropia among children before 6 years of age. Infants with significant astigmatism have an increased risk of anisometropia. The prevalence of anisometropia increases between 5 and 15 years, when some children's eyes grow longer and become myopic. However, anisometropia was found to accompany both myopia and hyperopia, suggesting that other mechanisms in addition to excessive eye growth may exist for anisometropia development, especially in hyperopia.

Acknowledgments

We thank all participants in our longitudinal study and their families.

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